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CME Activity

Effective Treatment Strategies for the Management of Diabetic Macular Edema

Nancy Holekamp, MD, moderator
Alexander M. Eaton, MD
Matthew Ohr, MD
Charles C. Wykoff, MD, PhD

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TARGET AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Discuss the advantages and disadvantages of anti-VEGF therapy for patients with DME
- Recognize the clinical benefits of intravitreal steroid implant therapy, especially in patients that are refractory or have persistent DME
- Discuss the treatment of DR in the setting of DME with steroids
- Outline a patient-centric treatment protocol for the treatment of DME

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Nancy Holekamp, MD, moderator
Pepose Vision Institute
St. Louis, Missouri

Alexander M. Eaton, MD
Retina Health Center
Fort Myers, Florida

Matthew Ohr, MD
Havener Eye Institute
Columbus, Ohio

Charles C. Wycoff, MD, PhD
Retina Consultants of Houston, Blanton Eye Institute
Houston, Texas

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Effective Treatment Strategies for the Management of Diabetic Macular Edema

Medical therapies have reduced the severity of diabetic macular edema (DME) and diabetic retinopathy and timely treatment can reduce severe vision loss by 90%.[1] Treatment options for DME include intravitreal anti-VEGF injections, focal/grid macular laser surgery, and corticosteroids that are either injected or implanted into the eye. These treatments can be used alone or in combination therapy to treat DME. However, DME is difficult to manage and many patients do not respond to first-line therapies. Even the patients that respond require multiple monthly treatments and many still have persistent DME.[2,3]

Intravitreal steroid implants such as dexamethasone and fluocinolone acetonide play a key role in reducing the inflammation associated with DME, and do not require monthly re-treatment.[1] Although dexamethasone and fluocinolone acetonide implants have been associated with cataract and intraocular pressure elevation,[4-6] clinical studies including MEAD/CHAMPLAIN and FAMOUS/FAME studies demonstrate that these agents play a significant role in the management of DME especially in patients with refractory DME.[1,7-13]

—Nancy Holekamp, MD, moderator

EPIDEMIOLOGY OF DME

Alexander M. Eaton, MD: The number of patients with diabetic macular edema (DME) is gradually increasing. This is largely due to the increased incidence of type 2 diabetes.

Nancy Holekamp, MD: Why do we see DME more in type 2 diabetic patients?

Dr. Eaton: Our understanding of DME is increasing, and we are beginning to realize that it is more than just a VEGF-driven disease. It is now well recognized that inflammation plays an important role in the development of DME. That is part of what is driving the growing incidence of diabetic retinopathy (DR) in the type 2 patients.

Dr. Holekamp: Type 1 diabetes might have a different time course, or a different interplay of these cytokines or interleukins. Do you think that the duration has anything to do with that?

Charles C. Wykoff, MD, PhD: Yes. While type 2 is much more common than type 1, overall type 1 is associated with more frequent and more severe ocular complications.[14] Long-term epidemiologic studies indicate that a majority of diabetics, regardless of type 1 or 2 designation will develop DR and a substantial proportion of these will develop DME.[15] I frame the issue of development of DR for my patients as a *when* not an *if* question.

Dr. Holekamp: So, we need to be vigilant for both type 1 and type 2 diabetics. We need to look for and treat DME.

Dr. Wykoff: Certainly, and the broader concept of DR management. I think we have focused as a community on the treatment of DME and proliferative DR (PDR), and I think that we are just beginning to appreciate the importance of managing nonproliferative DR even in the absence of DME.

DME TREATMENT OPTIONS AND IMPACT ON DR

Dr Holekamp: Some of our interventions for DME can actually reverse DR. What are your thoughts?

Dr. Eaton: Our understanding of the benefits of anti-VEGFs and intravitreal steroids, in terms of modulating not only DME but DR, is growing. There are advantages in terms of visual acuity and peripheral vision to using medications over laser therapy. However, relying solely on medication can result in the risk of progression of

DR that can be quite problematic when patients fail to return for regular follow-up, and we know that our diabetic patients are not as compliant as other patient groups. For effective management, it is preferable to use a combination of medications and appropriate laser to try to reduce the risk.

Dr. Holekamp: You talked about laser being kind of a long-term maintenance program for people who may have sporadic follow-up. You also noted that many of our interventions for DME can reverse some of the phenotypic signs of DR. There is an increased emphasis on the anti-VEGF agents for reversing DR. Dr. Wykoff recently finished a study using long-term corticosteroid drug delivery that also shows the same thing or similar results.[16]

Dr. Wykoff: Slowing the progression of DR is incredibly important. There is now data to show that steroids can slow the progression to PDR with similar efficacy as that obtained with anti-VEGFs. The best data we have is from the prospective, randomized phase 3 FAME A and B studies, in which a mean of 1.3 to 1.4 intravitreal injections of the fluocinolone acetonide implant were given over 3 years for the treatment of DME incompletely responsive to focal macular laser.[8,17] In the complete data set, through the primary endpoint of 2 years and then 3 years, 26% and 31% of sham-controlled eyes progressed to PDR; fluocinolone treatment significantly reduced the rate of progression to PDR with 12% to 13%, and 17% to 18% of treated patients progressing to PDR at 2 and 3 years.[16] The magnitude of this blunted progression to PDR appears similar to that observed with monthly anti-VEGF therapy, although anti-VEGF and steroid treatments have not been directly compared in a head-to-head study.[18] Demonstrating one can slow progression to PDR with steroids with a reduced treatment burden is great and needs further study.

Dr. Holekamp: Were you surprised that long-term corticosteroid delivery can blunt the progression of DR?

Dr. Eaton: No. In the patients I have treated with the fluocinolone acetonide intravitreal implant, I have seen excellent control of their DR. Interestingly, despite the fact that some patients have extensive ischemia, their DME has responded better to the fluocinolone acetonide intravitreal implant than the anti-VEGF therapy, and their DR has been well controlled as well. I think Dr. Wykoff's results are really powerful and suggest the fluocinolone acetonide implant can play an important role in not only the control of DME but of their DR as well.

Matthew Ohr, MD: This was one of the late-breaking developments at the American Academy of Ophthalmology meeting last year.[16] It is a very interesting change to the treatment dynamic to have an option for a longer acting agent. If patients receive an intravitreal long-acting agent and they have edema in follow-up, I feel a lot more comfortable watching them if they are actually receiving continuous treatment.

> "If patients receive an intravitreal long-acting agent and they have edema in follow-up, I feel a lot more comfortable watching them if they are actually receiving continuous treatment."
>
> *—Matthew Ohr, MD*

Dr. Holekamp: Some retina specialists prefer an anti-VEGF agent for treating DME because it can reverse DR or preclude the ongoing worsening to PDR. They use anti-VEGF agents in deference to corticosteroids. As Dr. Ohr mentioned, we heard at the American Academy of Ophthalmology meeting that corticosteroids could also delay the progression to PDR. Do you think this will have an impact on drug selection?

Dr. Ohr: Well, there is no question anti-VEGF agents still remain the first-line treatment. The biggest difference is alternative treatments for patients who are refractory. I think as more data comes out, and as we see some of these changes that take place, it will allow for more a data-driven discussion on how steroids play a role. We know that this is a multifactorial disease. If the patient is not responsive to anti-VEGF, then we need to look at alternative treatments.

TREATMENT ALGORITHMS FOR DME

Dr. Holekamp: What are your treatment algorithms, given the latest data?

Dr. Wykoff: For patients who have center-involved DME with visual acuity loss and are symptomatic, I start with an anti-VEGF agent. I see how they respond. I used to give six, nine, maybe even 12 injections at monthly intervals in the presence of persistent edema. However, the time point at which I have begun to add alternative therapies, and/or combination therapies, is shifting earlier. The thought process is, if I am not getting a robust response after three to four injections and the patient is still symptomatic and the vision is still not where I and the patient want it to be, then I will consider

alternative agents attempting to maximize their visual acuity potential as efficiently as possible. If we look at the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T data in aggregate, for example, more than 50% of patients met criteria for focal macular laser therapy at some point.[19,20] This means that the anti-VEGFs were incompletely drying the retinas in a majority of patients.

Dr. Eaton: I have a treatment algorithm that is very similar with one exception: I tend to look at each patient's overall health picture, which I factor into my decision-making. Many of the patients whom I see in Florida tend to be older and there are a lot of comorbidities associated with type 2 diabetes in this patient population.

For a patient without vascular risk factors but with center-involving DME, I am going to start with anti-VEGF therapy and see how they respond. I would proceed similarly with the younger patients because we do not want to increase the risk of cataracts, and many of them respond favorably to anti-VEGF therapy. However, if I have a patient with a history of a heart attack, stents, a stroke, and/or TIAs, my discussion with that patient is going to be quite different. Recent papers by Robert Avery, MD,[21] and Matthew Schlenker, MD,[22] suggest that the use of anti-VEGF therapy may contribute to an increased risk of cerebrovascular accident, death, and/or thromboembolic events. In these at-risk patients, the potential of a cataract, glaucoma, or pressure elevation is not as concerning as the risk of death or a vascular event because they are manageable. In this group, when there is center-involving DME, I tend to start with a steroid implant rather than anti-VEGF therapy to minimize the anti-VEGF risks and to try and get a prompt improvement in vision. In those with extrafoveal DME and reasonably good vision, I would also consider starting with focal laser.

Dr. Holekamp: Should we be identifying a subgroup of patients for whom laser or corticosteroids would be first-line treatment?

Dr. Ohr: I think that the safety data on the anti-VEGFs is a topic that gets debated quite a bit. If systemic safety is a concern, I agree with Dr. Wykoff's suggestion to start with an implant in patients with cerebrovascular risk factors.

Dr. Holekamp: When we look at the current anti-VEGF clinical trials, which include Protocol I,[23] RIDE and RISE,[24] and even VIVID and VISTA,[25,26] their rescue therapy was laser. Is the concept of rescue therapy being laser current or outdated?

Dr. Wykoff: It is patient-dependent. If a patient is minimally responding to anti-VEGF therapy, I typically will consider using a steroid, but there are scenarios when I will use targeted macular laser.

Dr. Holekamp: Switch or add?

Dr. Wykoff: When I use a steroid in an eye incompletely responsive to anti-VEGF therapy, I typically switch to determine the efficacy of the different medications before I consider combining them. If I am adding focal laser to ongoing anti-VEGF therapy, then it is usually combination therapy. The eyes in which I consider using focal macular laser have clear causative microaneurysms well outside of the fovea on angiography.

FOCAL MACULAR LASER PHOTOCOAGULATION AS THERAPY FOR DME

Dr. Holekamp: What about the possibility that focal laser in and around the macula may actually harm vision?

Dr. Ohr: Ischemia is a key component that contributes to vision loss in diabetic patients. Therefore, I am a little bit more cautious about using focal laser in these patients.

Dr. Holekamp: Do you use fluorescein angiography (FA) in a similar way?

Dr. Eaton: I use FA in diabetic patients to get a better understanding of their underlying disease and the role that ischemia plays in it.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

Dr. Holekamp: Do you use optimal coherence tomography angiography (OCT-A) to help you assess the profusion status of the diabetic macula?

Dr. Wykoff: I have started doing more OCT-A in my diabetic patients. Initially, I used OCT-A primarily in age-related macular degeneration (AMD) and AMD-masquerade cases to evaluate for choroidal neovascularization. Current OCT-A machines do not give me an assessment of peripheral vascular status. When I obtain an angiogram in a diabetic patient, I am typically not using it just for analysis of the macula; I also use the peripheral ischemic burden to inform my decision-making.

Dr. Holekamp: With the use of OCT-A, I am wondering if we are going to see an improvement in the vasculature after anti-VEGF treatment and after corticosteroid treatments. Are we getting angiograms only at baseline? Or are we getting angiograms again in follow-up to look for improved perfusion or improved vascular status?

Dr. Eaton: It can be helpful, at times, in both cases, particularly in patients who have a large area of peripheral ischemia.

Dr. Holekamp: Does anyone use fluorescein to help assess the macula status? Do you also get fluorescein in follow-up visits to see how they respond to the treatment?

Dr. Ohr: I get it when I have patients who are not responding or who have vision changes I cannot explain.

Dr. Holekamp: Every diabetic patient who walks through the retina specialist's doors potentially gets an OCT. However, I can foresee a re-emergence of FA because of OCT-A without the injection. I can see it re-emerging as an important way to reassess response to treatment.

Dr. Wykoff: Does VEGF blockade have an effect on retinal vasculature in DR? I think there are good data to indicate that it does. The largest body of evidence comes from RIDE and RISE, in which VEGF blockade with monthly ranibizumab led to significant blunting of the development and progression of retinal nonperfusion within the macula.[27] However, within that dataset there is not a strong signal for reperfusion of nonperfused regions. Interestingly, analyses of much smaller clinical series have suggested marked improvements in peripheral regions of retinal nonperfusion with VEGF blockade in severely ischemic eyes.[28,29] More data are needed to better define the role of VEGF inhibition in altering retinal vasculature in retinal vascular diseases.

INTRAVITREAL ANTI-VEGF INJECTIONS

Dr. Holekamp: What is your treatment approach if you start with anti-VEGF?

Dr. Ohr: I use a patient-specific course. I give patients three to four baseline injections of anti-VEGF and then assess their response. In those patients who did not respond, I will change to intravitreal triamcinolone acetonide.

Dr. Holekamp: Are you familiar with the EARLY analysis of the Protocol I data?

Dr. Wykoff: The EARLY analysis was a post-hoc look at the DRCR.Net Protocol I data to see if one could predict long-term visual outcomes based on outcomes at a relatively early time point.[30] The two ranibizumab arms of Protocol I were pooled and visual acuity outcomes at week 12 (after three injections of ranibizumab) were used to predict outcomes at 1, 2, and 3 years. From a statistical perspective, the 12-week outcomes were a powerful predictive time point. If one considered patients who gained 10 letters or more at the 12-week point, those patients maintained their visual gains through 1 to 3 years. Conversely, those patients who gained less than 5 letters at week 12 continued to do poorly through 1 to 3 years as a population; suggesting that if patients have not gained much vision by 12 weeks, then they are unlikely to continue to gain vision without doing something different.

Dr. Holekamp: The EARLY analysis created a paradigm shift, because for the first time there was evidence that said after three anti-VEGF injections you could predict who was going to respond. What is interesting about the EARLY analysis is that there are correlations even after the first and second injections, but the error bars were larger.[30] And by the time you get to the third injection, the error bars were narrower and therefore more accurately predictive.

Dr. Eaton: Data from large Medicare database studies show us the number of injections our DME patients are getting is most likely below what they would need.[30] It was well below the every 4 to 8 weeks that many of the clinical studies show is beneficial, at least in the first year. We are most likely undertreating the diabetic population, but I think part of that is due to the patient's ability to come in for follow-up.

Dr. Holekamp: Would it surprise you that the 2015 Preferences and Trends (PAT) survey[31] showed that 40% of retina specialists reported that they were giving four to six injections in the first year of treatment for patients with DME? Another 40% reported that they were giving between two and three injections. What do you think is the reason?

Dr. Ohr: My concern would be that it is likely undertreatment. It just makes sense that continuous treatment would yield the best results for these patients.

Dr. Holekamp: How many anti-VEGF injections would or should patients receive in year 1?

Dr. Wykoff: If one considers the major anti-VEGF DME trials to date including RIDE and RISE,[24] VIVID and VISTA,[25] DRCR.net's Protocol I,[32] and DRCR.net's Protocol T,[19,20] on average it is somewhere between nine to 10 injections.

Dr. Holekamp: Well, we have RIDE and RISE,[24] VIVID and VISTA,[25] BOLT,[33] Protocol I,[23] and RESTORE[34] that all essentially say the same thing: A significant minority of patients had visual acuity improvement and met their primary endpoints with very frequent injections. But then that leaves almost a majority of patients who are not meeting these primary endpoints.

TREATING NONRESPONDERS TO ANTI-VEGF

Dr. Holekamp: So, why are some patients doing well with frequent anti-VEGF injections, and other patients are not?

Dr. Ohr: I think that speaks to the multifactorial pathophysiology of DR and DME. You are going to have nonresponders in that group because of other confounding variables like macular ischemia.

Dr. Holekamp: What causes a nonresponder?

Dr. Wykoff: There are factors that are modifiable and those that are not. If the macula in front of me is severely ischemic, that is not something I can modify with current treatments. In my mind, I need to take nonmodifiable factors off of the table and

focus on what can I affect—what I can impact to optimize their visual function. The most obvious thing we can do as retina specialists is look at the OCT. If there is persistent thickening despite ongoing anti-VEGF injections, then consider doing something different in attempt to achieve a better result.

Dr. Eaton: If you look at the populations in those studies, there were variations in terms of their initial visual acuity as they went into the study. Patients with better baseline visual acuity are going to be difficult to get an additional 3 lines. So, some of it has to do with stratification—patients who had poorer vision are more likely to get a better response. You have to be careful comparing each of the studies because they are different patient populations and enrolling criteria were different.

Let us analyze MEAD,[7,25] FAME,[8,11] VIVID and VISTA,[25] and RIDE and RISE.[24] We see similar rates of response; maybe a little bit higher in the aflibercept group. Basically, there was a doubling in MEAD.[7,35] We see that improvement is across the board through all of these various studies but trying to compare them directly is difficult.

When I see a new patient who has center-involving DME with a reduction in vision, I will give them anti-VEGF therapy and I will see them again in 5 weeks. A responder is somebody that has had a reduction in macular edema, generally associated with an improvement in vision. At that first visit, I am beginning to have a pretty good idea (without going three or four visits) whether or not a patient is responding. If there is not a reduction in the edema, and an improvement in vision, then I am really beginning to ask myself, is this really a responder?

Dr. Holekamp: After one injection?

Dr. Eaton: After one injection, if there is no improvement in the edema at 5 weeks, I do not want to wait to consider switching to corticosteroids. Many of the patients who are poor responders to anti-VEGF respond favorably to corticosteroid therapy. So if patients have a poor response, particularly if it is associated with significant functionally impairment, and they are not able to perform their daily activities, I might switch them after one treatment. In the EARLY study[30] a signal was seen on how they would respond long term to anti-VEGF therapy after one or two injections, and in poor responders I do not see the need to wait longer.

Dr. Holekamp: I think we have data across many different clinical trials, and even across disease states that if you wait you may not recover vision. Do you think we should move the needle earlier toward a change of therapy if we find a nonresponder?

Dr. Ohr: Going back in the EARLY trial,[30] looking at those initial treatments, and then evaluating the response, perhaps earlier treatment would be better. I just do not think we know how to guide that therapy. One of the things that I have learned in using anti-VEGF therapy is that sometimes a continued treatment, despite fluid and minimal response, has some secondary benefits.

Dr. Holekamp: Are you familiar with the independent investigator-sponsored study by Raj Maturi, MD, on using bevacizumab and dexamethasone implant in patients with DME?

Dr. Eaton: He compared patients who received ongoing therapy with bevacizumab versus ongoing therapy with dexamethasone intravitreal implant.[36] In more chronic patients there was better control of the macular edema with the steroid arm than with the bevacizumab arm. However, the visual acuity did not seem to differ. That really left me wondering why that was the case. It also raises the question if there is a little bit of DME and you have steroids in the eye, do we really need to treat the remaining edema? Are we treating their edema or are we treating their visual acuity?

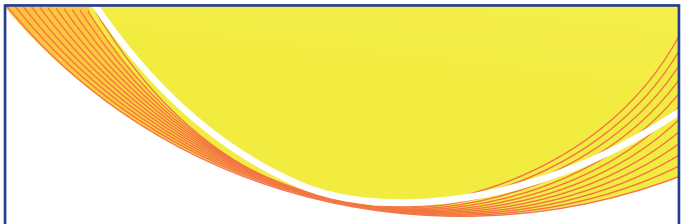
Dr. Holekamp: I had an opportunity to look at Dr. Maturi's study recently. He included patients who were receiving anti-VEGF monotherapy with bevacizumab. On average, they had had multiple injections, say 12 to 15 injections. These are patients with long-term anti-VEGF therapy who had an unsatisfactory response. At baseline of his study, they broke off into two arms, one that continued with bevacizumab, but then one that was randomized to continue bevacizumab with dexamethasone intravitreal implant. The anatomical result was improved with the dexamethasone intravitreal implant. However, the visual acuity was unchanged. If someone has received double digits of anti-VEGF therapy and then switched, have we lost the opportunity to gain vision? When do we have the opportunity to gain vision, and when might we wait too long and throw that away?

Dr. Ohr: Several studies have shown that the earlier that we can reverse the changes that are taking place, that is more beneficial. It does raise the point that when routine anti-VEGF injections are not accomplishing the goal we set out, maybe it makes sense to change treatment earlier.

CORTICOSTEROID USE IN DME

Dr. Holekamp: Where are we for the evidence-based medicine that supports corticosteroid use in DME?

Dr. Wykoff: Strong data exists to support the use of steroids for DME management. In Protocol I,[32] among pseudophakic eyes, preservative-free triamcinolone acetonide treatment achieved equivalent visual outcomes compared to anti-VEGF therapy at 1 year. If you take out the cataract effect, the treatments appeared very similar. The main challenge with the MEAD dataset[7,35] is that I think the dexamethasone implant arm was underdosed. To get an optimal anatomic and visual benefit, patients, on average, need dosing more often than every 6 months. Therefore, the MEAD



"Protocol I is still pertinent today, because in pseudophakic patients a single injection of triamcinolone acetonide over a 16-week period of time had equal efficacy to ranibizumab at 1 year."

—Nancy Holekamp, MD

data may not accurately reflect optimal outcomes if the dexamethasone implant was used according to need. In FAME,[8,11] we saw that the fluocinolone acetonide implant has a long duration of activity. In my own hands, the fluocinolone acetonide implant works well, although it does not have the immediate retinal-drying effect in some eyes as seen with the anti-VEGFs.

Dr. Holekamp: Protocol I[32] is still pertinent today, because in pseudophakic patients a single injection of triamcinolone acetonide over a 16-week period of time had equal efficacy to ranibizumab at 1 year. Triamcinolone acetonide is not a long-term drug-delivery system. We have two FDA-approved drug delivery systems right now. How often do you find you have to inject the dexamethasone implant to get maximum efficacy?

Dr. Eaton: We should dose it more consistently with patient's needs—say, every 2 to 4 months—and follow it more closely in a diabetic patient with resistant, difficult DME.

Dr. Ohr: The dexamethasone intravitreal implant offers another good option for treating DME. As we discussed before in the RISE and RIDE studies,[24] after 2 years of monthly ranibizumab injections, pronounced macular edema (evidenced by center thickness of > 250 microns on OCT) persisted in approximately 23% of patients. In these partial or nonresponders steroid therapy offers another therapeutic option. In addition, the longer duration of effect referenced by Dr. Holekamp in regard to the triamcinolone acetonide therapy in Protocol I[32] provides an opportunity for patients who may not have the flexibility or desire to receive monthly anti-VEGF injections. The extended-release dexamethasone intravitreal implant takes that further. In the MEAD trial[7,35] patients were dosed with the dexamethasone implant no more than every 6 months. With that interval, approximately 22% of patients saw an increase of greater than or equal to 15-letter improvement in BCVA. It is worth noting that these were patients with a mean duration of DME of approximately 24.9 months. In the trial, 66.6% of patients had received previous laser treatment for DME, 17.9% had been treated with intravitreal steroid, and 8.6% had been treated with anti-VEGF, and only 27.8% had received no previous treatment for DME. To your point about dosing, when you look at the subgroup analysis of mean vision change in pseudophakic eyes, there is a sawtooth-like fluctuation in the vision that suggests a pulse dose effect. The vision peaks 3 months after the dexamethasone is given and starts to decline in the fourth month. This is an effect I have seen clinically as well. It would be great to have an option to dose the dexamethasone implant more frequently, but most coverage plans only allow for 6-month dosing.

FLUOCINOLONE ACETONIDE IMPLANT

Dr. Holekamp: Do we see that pulse dose effect with the fluocinolone acetonide drug-delivery system?

Dr. Ohr: There is a much more linear effect with the fluocinolone acetonide treatment when you look at the metrics that were measured in the FAME[8,11] data.

Dr. Holekamp: In FAME,[8,11] how often were patients re-injected with a fluocinolone acetonide implant?

Dr. Wykoff: The average number of injections was 1.3 to 1.4, a treatment burden different than repeated anti-VEGF injections through 3 years. I think the Europeans have adapted the fluocinolone acetonide implant more readily than American retinal physicians. The on-label nearly 5% risk of surgical intervention for elevated IOP is a concern for a lot of physicians. Importantly, analyses of the FAME data found that no patients treated with the fluocinolone acetonide implant who received prior ocular steroids required IOP-lowering surgery.[37] Ruling out steroid-responsiveness with a course of steroids before using the fluocinolone acetonide implant is an important step to minimize risk. We need more real-world data from the United States to better define the clinical risk of IOP elevation with the fluocinolone acetonide implant.

Dr. Holekamp: We mentioned the obvious undertreatment of dexamethasone intravitreal implant in MEAD.[7,35] We know undertreatment is a concern with the anti-VEGFs, and now it appears that both of those modalities are susceptible to undertreatment. In contrast, the data seem to be very different for the fluocinolone acetonide implant. We do not feel that patients were undertreated in FAME,[8,11] and they did not require additional treatments. Do those patients still require close follow-up? What is your opinion on the durability and sustainability of the fluocinolone acetonide implant?

Dr. Eaton: The fluocinolone acetonide implant has a durable release over 3 years. The difference between the fluocinolone

acetonide implant and dexamethasone intravitreal implant is that the latter delivers a much higher dose of corticosteroid to the eye. It is still a pulse. When do you re-treat with a dexamethasone intravitreal implant? Is it at 2 to 4 months? If you want to keep patients dry, you probably have to treat them on a shorter basis.

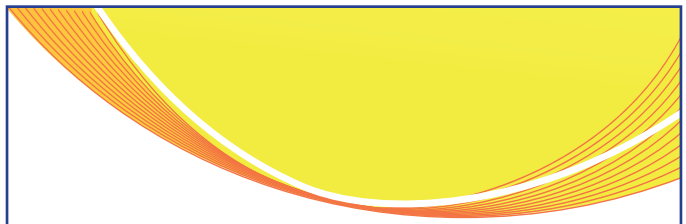
With some of the patients with more resistant DME, the fluocinolone acetonide implant may leave them with recurrent and/or persistent edema. In these patients, anti-VEGF therapy has been very successful. In patients with recalcitrant DME, a second fluocinolone acetonide implant can also be considered after 1 year in patients without IOP problems.[10]

Dr. Holekamp: Do you find that patients are largely well-controlled and that is all they need? Or do you find that through your quarterly monitoring that they may need additional supplementary therapy?

Dr. Ohr: Both, I have seen patients who have excellent control with fluocinolone acetonide treatment in isolation, and I also have patients who recur with DME despite the treatment. What is interesting is there are various strategies. The implant is a continuous low-dose baseline treatment. Maybe there are patients who sometimes need a little booster, and that booster may be anti-VEGF treatment, or even a repeat treatment with the fluocinolone acetonide intravitreal implant or a triamcinolone acetonide injection. In contrast to anti-VEGF, once I have the fluocinolone acetonide implant in, I know that they are still getting a low-dose continuous treatment. And I feel better about that.

In other treatment modalities, my concern is that edema is just going to continue to get worse if the patient is not treated on the day I see them. It is important to remember the steroid treatments are different. The triamcinolone acetonide and dexamethasone intravitreal implant have a much different potency than the fluocinolone acetonide implant does. With the first two, we expect edema will respond immediately, but the fluocinolone acetonide implant is a much lower and continuous dose treatment. It may take 2 or 3 months before the treatment effect is noticeable. In some of my patients, edema improved but only slightly in that first or second month, but if I waited another 2 to 3 months, I get the affect and resolution I am expecting.

Dr. Wykoff: From both RISE and RIDE[24] and VISTA and VIVID,[25] we saw signals that earlier treatment of DME led to better outcomes,[24,25,38] suggesting that persistent edema may be detrimental. Now we are considering that because we have a low-dose steroid on board, this paradigm may be different. To address this, we would need a trial in which DME eyes treated with fluocinolone acetonide with persistent fluid were randomized to observation versus anti-VEGF supplementation. Until we have data informing this issue, I am a little uncomfortable watching eyes indefinitely that have a fluocinolone acetonide implant in the presence of persistent DME. I do not mind waiting a couple of months, but I have a relatively low threshold to supplement with anti-VEGF therapy.



"In patients with recalcitrant DME, a second fluocinolone acetonide implant can also be considered after 1 year in patients without IOP problems."

—Alexander M. Eaton, MD

Dr. Holekamp: I have even supplemented with a dexamethasone implant on top of the fluocinolone acetonide just for this type of exacerbation of intraretinal fluid, and it works. You need a little pulse from time to time. However, we need more data to guide us in these situations, and hopefully we will get that soon.

ADDRESSING CORTICOSTEROID SAFETY

Dr. Holekamp: We are all using corticosteroids in our patients with DME. We all recognize that they carry with it this risk of elevated IOP and cataract. Can you tell me about the safety profile of corticosteroids?

Dr. Eaton: There is concern about the 4% to 5% reported risk of IOP related to surgery in the low-dose arm of the FAME study.[8,11] However, the risk with the fluocinolone acetonide intravitreal implant is less than you would anticipate. In the group that had received prior steroids in the FAME study and did not have a significant increase in IOP after the steroids, none went on to require incisional surgery to reduce IOP. It is this finding that led to the FDA approval guidelines, which very nicely preselects the patients who are least likely to develop a steroid-induced pressure elevation. The flip side of that is the MEAD study underdosed, so we need to be cautious about comparing the percentage of patients requiring incisional glaucoma surgery between the two studies.[7,35] I think if you dose the dexamethasone intravitreal implant at a frequency sufficient to prevent recurrent fluid, the incidence of steroid-induced incisional surgery will more closely resemble the rate seen with the fluocinolone acetonide implant in the FAME study.

Dr. Holekamp: Earlier we discussed adding or switching to a corticosteroid after three injections with an anti-VEGF, and perhaps even using corticosteroids in a select subgroup of patients as

a first-line therapy. Are you concerned about creating more glaucoma and cataracts for our diabetic patients?

Dr. Ohr: Clearly we know the side effect profile of steroids is potentially induced cataracts and also, in some patients, increased IOP. I tend to challenge my patients who are under consideration for the fluocinolone acetonide intravitreal implant with intravitreal triamcinolone. About 60% of patients, at least in the FAME data,[8,11] will not have an IOP response. And then 35% to 40% of those patients who do have a pressure response can be managed with topical therapies. I think the steroid challenge is important because it lets you know ahead of time which patients may be cause for concern.

REFERRALS TO SPECIALISTS

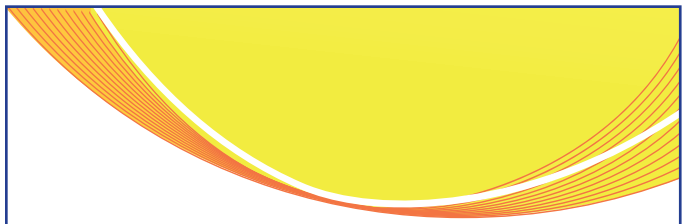
Dr. Holekamp: How frequently do you follow patients looking for this increased IOP? Are you managing it yourself or do you refer your patients?

Dr. Wykoff: Patients need to be informed not only about the duration of the medication that you are using, but also the potential risks. About a third of the patients given an ocular steroid are going to have an IOP response. The majority of those can be controlled medically, and I like to comanage these patients with my referring doctors. When I identify a patient with an IOP response to an ocular steroid, depending on the level of IOP rise, I may prescribe an IOP-lowering drop and have the patient see their referring doctor for continued IOP management.

Dr. Eaton: I take a similar approach to Dr. Wykoff. After a fluocinolone acetonide implant, I use a follow-up regimen similar to that employed in the FAME study. In FAME,[8,11] patients were seen at 1 and 6 weeks, and then every 3 months. By following this regimen, IOP-induced optic nerve damage should not occur, provided patients are treated should a pressure elevation develop. Prior to treatment, I confirm that they are willing to follow this regimen. If not, I consider alternative treatments. It is also helpful to let our comanaging ophthalmologists know that in FAME[8,11] some patients had a pressure elevation.

Dr. Holekamp: What about cataracts? Are we hesitant to use corticosteroids for DME in these younger diabetic patients who are still phakic? Are cataracts just assumed to be a complication? What is your approach to phakic patients with DME, and what do you tell them about their cataract?

Dr. Ohr: That is a discussion that we have prior to any treatment, especially with steroids. The conversation I generally have with my patients regarding cataracts is that if the cataracts do arise that they are treatable. There are certainly risks with cataract surgery, but there are always risks for diabetic patients undergoing any type of surgery. Cataracts can be treated and the vision returned; in contrast, the damage done by DME is not reversible.



"Eyes with pre-existing DME are at elevated risk of pseudophakic cystoid macular edema, and pretreatment with a steroid implant appears to be protective of this response."

—Charles C. Wykoff, MD, PhD

It is extremely important that we address DME as a priority. I am more concerned with the status of the retina if the DME is allowed to persist for too long.

Dr. Holekamp: Yes, managing DME needs to take precedence over the potential development of a cataract. In the corticosteroid studies, how did the patients who subsequently underwent cataract surgery, do? Were they harmed by the cataract surgery?

Dr. Wykoff: We have good data to indicate that no, cataract surgery did not harm patients being treated for DME with steroids. In MEAD,[7,34] dexamethasone treatment appeared to be protective of a postoperative macular edema increase. In the control, nondexamethasone-treated eyes, macular edema increased significantly following cataract surgery, a fluctuation that was not observed among the dexamethasone-treated eyes. Eyes with pre-existing DME are at elevated risk of pseudophakic cystoid macular edema. and pretreatment with a steroid implant appears to be protective of this response.

Dr. Holekamp: What about FAME?

Dr. Eaton: FAME showed the same thing.[8,11] Patients who had cataract surgery after insertion of the fluocinolone acetonide intravitreal implant did well postoperatively. After the cataract was taken out, the data showed that there was no difference between that group and the pseudophakic group in terms of their eventual visual outcome.

Dr. Holekamp: A few words on what your take-home message is for an effective treatment strategy for DME?

Dr. Ohr: DME needs to be treated and treated aggressively. The addition of long-term dosing strategies gives us just another tool

to use in patients with DME. My personal approach is treating them with anti-VEGF treatments in order to quickly reverse the DME. In patients who are treatment-resistant to the anti-VEGF, I start to consider corticosteroids. The long-acting corticosteroids as treatment strategies may be very beneficial. There is certainly a lot of hope on the horizon that the combination treatment strategies of the steroid and the anti-VEGFs may improve upon the results that we already have discussed.

Dr. Wykoff: DME is a heterogeneous disease and requires a patient-specific approach. In general, anti-VEGFs are my first-line management strategy. I consider a corticosteroid early in the management of center-involved DME when anti-VEGFs appear incompletely effective. Focal laser can be valuable in specific patients. Because we have data that long-term fluid exposure probably leads to less-than-optimal outcomes, my goal is to dry the retina as efficiently as possible with as few side effects as possible.

Dr. Eaton: There is growing evidence that inflammation plays an important role in the development of DME. In selecting the optimal treatment for any patient, we really need to base our decision on that patient's specific needs and risk factors. My general preference is to proceed with anti-VEGF therapy unless the patient has significant arterial thromboembolic risk factors. In that case, I might move to steroids as a first-line therapy and may consider laser. For those treated with anti-VEGF, I will be reasonably quick to treat patients who appear to be poor or nonresponders with corticosteroids. The treatment really evolves from there depending on the patient's needs. We need to determine how they are responding so as to minimize their edema while at the same time maximizing their vision. I like having a lot of new options to help me better manage these patients and to try to get them better outcomes.

Dr. Holekamp: In conclusion, in the current treatment of DME, anti-VEGF agents remain first-line therapy. Laser may be an adjunct, but the rescue therapy for nonresponders is likely corticosteroids. It is probably better to move away from a partially effective or noneffective therapy to something that might be more effective, and to do so earlier rather than later in our treatment paradigms. We have lots of good evidence for monotherapy with each of these agents, but we really lack data to support a combination therapy that may be a bonus for our patients.

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EFFECTIVE TREATMENT STRATEGIES FOR THE MANAGEMENT OF DIABETIC MACULAR EDEMA
CME QUESTIONS

1 *AMA PRA Category 1 Credit*™ Expires September 2017

1. What were the key findings from the EARLY study?
- a. If patients do not respond after three anti-VEGF injections, physicians should consider other treatment strategies
- b. If patients do not respond after one anti-VEGF injection, physicians should consider other treatment strategies
- c. If patients do not respond after five anti-VEGF injections, physicians should consider other treatment strategies
- d. There was no significant differences in response time based on anti-VEGF treatment frequency

2. What is the key advantage of steroid implants in a diabetic patient population?
- a. Do not require frequent injections
- b. Reduced IOP
- c. Reduced ischemia
- d. Does not require follow-up

3. In Protocol I, the triamcinolone arm was _____ at 1 year in pseudophakic eyes.
- a. Significantly better than the anti-VEGF arm
- b. Significantly worse than the anti-VEGF arm
- c. About the same as the anti-VEGF arm
- d. Better than laser, but worse than the anti-VEFG arm

4. Package inserts for fluocinolone acetonide implant note a _____ rate of surgical intervention for elevated IOP.
- a. 1%
- b. 3%
- c. 5%
- d. 8%

5. According to the panelists, what is the first-line treatment option for DME?
- a. Corticosteroids
- b. Laser
- c. Combination therapy
- d. Anti-VEGF injections

6. What are some of the factors that cause a patient to be a nonresponder to anti-VEGF injections in DME?
- a. Ongoing ischemia
- b. Youthful age at presentation
- c. Presence of proliferative diabetic retinopathy
- d. Comorbidity with glaucoma

7. What was the percentage of 3-line gainers in visual acuity outcomes at month 24 in the phakic group treated with fluocinolone acetonide in the FAME studies?
- a. 13%
- b. 23%
- c. 29%
- d. 37%

8. What was the key finding of the MEAD study?
- a. Dexamethasone intravitreal implant improved the long-term BCVA with no increases in IOP and cataract development
- b. Dexamethasone intravitreal implant improved the long-term BCVA with modest increase in IOP and cataract development
- c. Dexamethasone intravitreal implant improved the long-term BCVA with significant increases in IOP and cataract development
- d. Dexamethasone intravitreal implant improved the long-term BCVA without increases in IOP

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the advantages and disadvantages of anti-VEGF therapy for patients with DME	_____	_____	_____
Recognize the clinical benefits of intravitreal steroid implant therapy especially in patients that are refractory or have persistent DME	_____	_____	_____
Discuss the treatment of DR in the setting of DME with steroids	_____	_____	_____
Outline a patient-centric treatment protocol for the treatment of DME	_____	_____	_____

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

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Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

Please identify how you will improve/change: _____

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_____

If no, please identify the barriers to change.

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